09/914178

WO 00/49994 PCT/US00/04442

AN AQUEOUS NON-ALCOHOLIC ORAL RINSE CONTAINING BENZOCAINE AND CARBOMER

Field of the Invention

The instant invention relates to an oral rinse. More specifically, the instant invention relates to an aqueous non-alcoholic oral rinse that contains benzocaine and carbomer.

Background Art

Oral rinse (mouthwash) compositions have been used for many years to prevent bad breath and eliminate bacteria and other microorganisms responsible for bad breath, tooth decay, plaque and gum diseases (such as gingivitis and periodontis). Conventional oral rinses generally contain high levels of an alcoholic solvent such as ethanol (percentages may range anywhere from approximately 10% to about 30% by volume). The alcoholic solvent serves as a disinfectant, a preservative, and as a dispersant for other additives.

However, the use of alcohol has a number of undesirable physical effects. Chronic exposure to alcohol has been found to result in gum "burn." In addition, persons afflicted with dry-mouth syndrome must avoid alcohol because it removes moisture from the oral tissues, thereby aggravating the condition. Furthermore, there is a concern that children can be adversely affected by inadvertently swallowing alcoholic oral rinse compositions.

There are also a number of societal concerns that make the use of alcohol undesirable. For example, persons of certain religious beliefs may not ingest alcohol in any form. Furthermore, recovering alcoholics are advised to avoid all alcohol containing oral compositions.

Several attempts at formulating non-alcoholic mouthwash compositions can be found in the prior art. Examples of such compositions include U.S. Patent Nos. 5,817,295; 5,723,106; 5,707,610; 5,560,906; 5,407,664; 5,292,527; and 4,919,918. None of the disclosed compositions contain benzocaine, a compound used to treat aphthous ulcers. This is because benzocaine is only slightly soluble in water.

Aphthous ulcers, often referred to as canker sores, are characterized by painful eruptions in the mucous membrane of the mouth. Of unknown etiology, these sores are covered by a grey/white exudate and surrounded by a reddened area. They range in size from several millimeters to two centimeters in diameter. The ulcers are limited to oral mucous membranes not bound to periosteum, e.g., the inner portion of the lip or cheek. Aphthous ulcers may occur as solitary or multiple lesions. Generally, these ulcers heal spontaneously in one or two weeks.

Therapy for aphthous ulcers and mouth sores generally involves the use of a topical anesthetic such as benzocaine. Benzocaine can be dispersed in aqueous oral rinses by using alcoholic solvents such as ethanol. However, benzocaine is only sparingly soluble in water alone. According to the Merck Index, "One gram dissolves in about 2500 mL water," or only 0.04% w/v. Prior to this invention, it has not been possible to disperse benozocaine in an aqueous media (beyond the very low level identified by the Merk) absent the use of alcoholic solvents. Thus, a non-alcoholic aqueous oral rinse containing effective amounts of benzocaine to treat ulcers has not been possible.

Summary of the Invention

The invention is directed to an aqueous non-alcoholic oral rinse that contains benzocaine in a sufficient amount to relieve the soreness of aphthous ulcers and similar mouth sores. It has been discovered that a carbomer can be used to effectively disperse the benzocaine into a non-alcoholic aqueous solution.

The essential ingredients of the composition are benzocaine, carbomer, and water. However, a neutralizing agent is preferably employed to "over-neutralize" the carbomer, and thereby generate a transparent solution. In addition, various additives commonly employed in the oral rinse art may be employed that include preservatives, antibacterial agents, buffering agents, surfactants, sweetening agents, flavoring agents, humectants, emulsifiers, and colorants.

Disclosure of the Invention

The invention is an aqueous non-alcoholic oral rinse that contains benzocaine in a sufficient amount to relieve the soreness associated with aphthous ulcers and similar mouth sores. By the term "aqueous" it that meant the predominant solvent in the system is water. By the term "non-alcoholic" it is meant that aliphatic alcoholic solvents such as ethanol are not present in the composition.

The first essential component of the oral rinse composition is benzocaine ($C_9H_{11}NO_2$). Benzocaine is a known anesthetic that is also known as ethyl amino benzoate and p-aminobenzoic acid ethyl ester. Benzocaine is added in an amount above 0.04%, and preferably above 0.07% by weight of the oral rinse. Preferably, benzocaine is employed in "sub-therapeutic levels" - meaning levels below the amount typically used in OTC Drug applications (5% by weight or more). Thus the most preferred range of benzocaine in the oral rinse is between 0.04% and 5% by weight.

The second essential component of the invention is a polyacrylic acid of the type sold by B.F. Goodrich under the tradename Carbopol®. The USP-NF, the British Pharmacopoeia, the United States Adopted Names Council (USAN), and the Cosmetic, Toiletries and Fragrance Association (CTFA), have all adopted the generic (i.e., nonproprietary) name "carbomer" for the Carbopol® polymers. Carbomers fall into the following two catergories: (1) homopolymers of acrylic acid crosslinked with allyl sucrose, polyalkyl ethers of divinyl glycol, or ally pentaerythritol; and (2) similarly crosslinked copolymers of acrylic acid with minor levels (less that 10% by weight) of long chain alkyl acrylate comonomers. A carbomer's acrylic acid content is generally 90% or more, by weight. The preferred acrylic acid monomer used to make a carbomer is the actual compound "acrylic acid." However, other acrylic acids can also be employed, e.g. methacrylic acid and C_{1-4} alkyl substituted acrylic acid.

The most preferred carbomers include the products Carbopol® ETD™ 2001, Carbopol® ETD™ 2020, and Carbopol® ETD™ 2050. These "easy-to-disperse

(ETD™)" carbomers are homopolymers or copolymers of acrylic acid, produced using a polymerization aid, and crosslinked with a polyalkenyl polyether. Carbopol® ETD™ 2001, Carbopol® ETD™ 2020, and Carbopol® ETD™ 2050 are easier to disperse and mix than other Carbopol® products. The carbomers wet quickly and thereby minimize lumping. By "wet" it is meant that the white particles of polymer fully disappear (disperse) into the mixture. The carbomers also hydrate slowly and have a lower viscosity prior to neutralization than other Carbopol® products. Because of the fast wetting nature and low viscosity of these carbomers, vigorous agitation is not necessary to disperse them. The fast wetting nature of these carbomers also aids handling. The most preferred carbomer is Carbopol® ETD™ 2050.

The amount of carbomer used is not particularly limited. However, it is preferred that the carbomer be used in an amount of no more than 10% by weight and represent approximately ½ the total weight of the benzocaine employed.

It has been discovered that even though benzocaine is only sparingly soluble in water (0.04% w/v), it can be carried into solution as a neutralizing agent for the carbomer. The amine portion of the benzocaine acts by neutralizing the carbomer and is carried by the finely dispersed carbomer into solution, forming a hazy liquid dispersion. An aqueous solution containing carbomer alone generally has a pH around 1.2. When benzocaine is added the pH approaches neutrality.

Preferably, a small amount of a second neutralizing agent is also added. The second neutralizing agent is added to "over neutralize" the carbomer - meaning that the pH is brought to 8.0 or higher. This serves to break down the carbomer's chain length and reduce its viscosity and, thereby, eliminate the haziness of the dispersion to create a transparent solution. The most preferred neutralizing agent is triethanolamine. When neutralizing agents are employed in addition to the benzocaine they are generally present in an amount ranging from .001 to 3% by weight of the oral rinse. Preferably, the neutralizing agents are present in the amount of approximately 1.5% by weight of the oral rinse.

In addition, a number of conventional oral rinse additives can also be employed. These additives include preservatives, weak carboxylic acids, antibacterial agents, buffering agents, surfactants, sweetening agents, and flavoring agents.

Preservatives prolong the useful life of the composition. Sodium benzoate is by far the most preferred preservative. Sodium benzoate is also effective in inhibiting microorganisms in the formulations described above. An effective concentration range for sodium benzoate in the composition of the present invention is generally from about 0.05% to about 0.2% by weight with the most effective level being about 0.1% by weight. Although sodium benzoate is the most preferred preservative, alternative or additional preservatives, such as methylparaben may also be used. Generally, the total amount of preservative employed represents no more that 0.5% by weight of the total oral rinse.

Weak carboxylic acids primarily serve as acidulants but also contribute antibacterial activity to the composition in a synergistic manner with sodium benzoate. Examples of suitable weak carboxylic acids include citric acid, tartaric acid (D, L, DL, or a mixture thereof), acetic acid, and benzoic acid. The most preferred carboxylic acid is citric acid. Preferably, the carboxylic acid should be present in the composition at a concentration of from 0.01% to about 1.0% by weight of the total with the most desired level being about 0.1%.

The synergistic antibacterial properties of sodium benzoate in combination with the weak acid generally make the presence of additional antibacterial agents unnecessary. However, additional antibacterial agents may always be added. Antibacterial agents include phenolic compounds such as β-naphthol, thymol, chlorothymol, amyl-, hexyl-, heptyl- and octylphenol, hexylresorcinol, hexachlorophene, and phenol; quartenary ammonium compounds such as quartenary morpholinium alkyl sulfates, cetylpyridinium chloride, alkyldimethyl benzylammonium chloride, and alkyltrimethyl ammonium halides. In addition, miscellaneous antibacterial compounds may be employed such as benzoic acid, formaldehyde, potassium chlorate, tyrothricin, gramicidin, iodine, sodium perborate, and

urea peroxide. The amount of antibacterial agent that can be added varies greatly with the particular antibacterial agent employed an should be evident to one of ordinary skill in the art. However, this agents, if employed, should never be the predominant non-aqueous ingredient in the composition.

Buffering agents adjust the pH of the final formulation. Generally, the buffering agent should be capable of bringing the pH to a physiologically acceptable level. Exemplary buffering agents are alkali metal and alkaline earth metal salts and amine (e.g., ammonium) salts of weak carboxylic acids. The preferred buffering agents are sodium citrate, potassium citrate, and sodium acetate. Preferably, the buffering agent should be present in the composition in a concentration of from about 2.0 to about 5.0% by weight of the total with the most desired level being about 2.75%.

Surfactants may be included in the composition to increasing the spreading properties of components in the solution, to keep the composition clear, and to prevent the composition from becoming turbid. Any food grade anionic, cationic or non-ionic surfactant can be employed. Preferably, the surfactants are nonionic surfactants. Particularly preferred nonionic surfactants are polysorbates. Polysorbates are polyoxyethylene fatty acid esters. Polysorbates are obtained by the esterification of sorbitol with a fatty acid such as stearic acid, lauric acid and palmitic acid under conditions that cause the splitting out of water from sorbitol, leaving sorbitan. About 20 moles of ethylene oxide per mole of sorbitol are used in the condensation to effect water solution. Suitable polysorbates include polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), polysorbate 65 (polyoxyethylene (20) sorbitan tristearate), and polysorborbate 80 (polyoxyethylene (20) sorbitan monooleate). The most preferred surfactant is polysorbate 20. When surfactants are employed, they are generally present in an amount of at least 0.001% and no more than 3%, based on the entire weight of the oral rinse. Preferably, the surfactants represent

0.001% to 1% of the oral rinse. Most preferably, the surfactants are 0.001% to 0.5% of the oral rinse.

Sweetening agents may be included in the composition to sweeten the taste of the composition. While sodium saccharin is the preferred sweetening agent, any food-use approved natural or artificial sweeteners are contemplated within the scope of the present invention. These sweeteners are, for example, sorbitol, xylitol, aspartame, and sucrose. When sodium saccharin is present in the composition it usually represents from 0.001% to 0.25% by weight of the total with the most desired level being about 0.1%. When employing a sweetening agent other than sodium saccharin any amount required to produce an equivalent level of sweetening as that obtained with sodium saccharin will suffice.

Flavoring agents may also be included in the composition. The flavoring agents can be selected from cinnamon, cassia, anise, menthol, methyl salicylate, peppermint oil, spearmint oil, and other known flavor modifiers. Particularly preferred are peppermint, spearmint oil (both natural and synthetic analog), and a mixture of the two. Flavoring agents are generally employed in the oral rinse at a concentration of from 0.001% to about 2.0% by weight of the total. More preferably, the concentration should be from about 0.05% to about 1.0% with the most desired level being about 0.2%.

Other miscellaneous agents may be added including humectants, emulsifiers, and colorants. A common agent is Amphosol (cocamidopropyl betaine). This chemical is often used in cleaning formulations and aids the cleaning and foaming properties of the oral rinse. Generally, Amphosol is employed in an amount no higher than 1.5% by weight and preferably less than 1.0% by weight of the total composition. Most preferably, Amphosol represents approximately 0.60% of the composition's weight.

The balance of the composition is water. Generally water represents at least 80% by weight, preferably at least 90% by weight, and most preferably about 94% by weight of the oral rinse. Water serves as the fluid base for the oral rinse composition.

The order of addition of the ingredients is important. One must first disperse the carbomer in the aqueous media. Then one must add an amount of benzocaine that is generally equal to two times the w/w% of carbomer. To this dispersion, additional oral rinse ingredients can be added and dissolved. A transparent oral rinse can be achieved by the addition of second neutralizing agent such as triethanol amine.

The following examples are intended to illustrate, but not limit, the invention:

Example 1 - Alcohol-Free Oral Rinse Containing Benzocaine

A preparation in accordance with the instant invention was prepared from the following components in the following amounts:

Part A (Oil Phase)	
Ingredient	%w/w
Polysorbate 20	0.12
Cocamidopropyl Betaine	0.60
Flavor	0.19
Carbopol ETD 2050	0.04
Benzocaine USP	0.08
Methylparaben NF	0.12
Part B (Water Phase)	
Ingredient	%w/w
Water, Purified	94.10
Sodium Citrate	2.78
Sodium Saccharin	0.09
Sodium Benzoate	0.11
Citric Acid	0.08
Triethanolamine	1.69
Total	100.00

The benzocaine in the above identified composition remains dispersed.

Example 2 - Alcohol-Free Oral Rinse Containing Benzocaine

Similar compositions to that described in Example 1 were made using other non-alcohlic organic solvents such as propylene glycol and polyethylene glycol instead of carbomer. In addition, compositions containing these organic solvents with emulsifiers such as polysorbate, pluronic, and cocamidopropyl betaine were prepared. In all of these preparations, only the amount of benzocaine roughly equivalent to that reported by the Merck (0.04 w/v) would solubilize. Additions beyond 0.04 g/100 mL water would precipitate out of solution in short order.

While the invention has been described in conjunction with the specific embodiments outlined above, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art. In example, some steps may be eliminated or performed ut of sequence. Accordingly, the preferred embodiments of the invention are intended to be illustrative and not limiting. Various changes may be made without departing from the spirit and scope of the invention as defined in the claims.